REMARKS

The claims pending are claims 1, 2, 4-15, and 21-26. Claims 3, and 16-20 stand canceled, without prejudice to refilling in a continuation application. Claims 1 and 11 are amended to clarify the target region of SEQ DI NO: 3 to which the claimed compound hybridizes. Dependent claims 21-26 add additional embodiments of claim 1. Support for these amendments may be found at specification pages 85-87 and specifically in Table 1.

Applicants further affirm the correctness of the inventive entity in view of the cancellation of claims. No new matter is introduced by this amendment.

Rejections Under 35 USC §112, first paragraph

> Claims 15-20 are rejected because the examiner considers that the specification is enabled for methods of inhibiting the expression of human stearoyl-CoA desaturase in cells or tissues *in vitro* using antisense, but does not provide enablement for *in vivo* methods.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

Cancellation of claims 16-20 moots this rejection as to them. Applicants make no comment on the validity of the rejection vis-à-vis claims 16-20. Applicants cancel these claims simply to advance prosecution of the remaining claims. Claim 15 has been amended to insert the words "*in vitro*". In view of these amendments, this rejection is satisfied and may be properly withdrawn.

Rejections Under 35 USC §102(b)

> Claims 1, 2, 11, 12 and 14 are rejected as being anticipated by International Patent Publication No. WO 00/09754 (Stenn). The examiner states that Stenn's 22-mer oligonucleotide primer is fully

complementary to SEQ ID NO: 3 and meets all of the structural requirements of the claims.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

Stenn's 22-mer oligonucleotide primer is similar to antisense sequence SEQ ID NO: 52 of the present invention, which sequence was never shown to have inhibitory activity. Stenn's primer and Applicants' SEQ ID NO: 52 are complementary to and hybridize with nucleotide positions 860 to 882 of SEQ ID NO: 3.

Applicants' claims are now limited to compounds that bind SEQ ID NO: 3 between nucleobases 771 to 843 or 1011 to 5040 thereof, which sequences fall outside of the sequence of SEQ ID NO: 3 to which the Stenn sequence can hybridize. In Table 1, Applicants demonstrate a selection of sequences that bind to the claimed regions of SEQ ID NO: 3 *to which Stenn's sequence cannot bind* and demonstrate inhibitory activity of 10% or above. Therefore, Stenn's primer cannot anticipate the claims as presently amended.

In view of these comments and the claim amendments noted above, this rejection may be properly withdrawn.

Rejections Under 35 USC §102(e)

Claims 1, 2, 11, 12 and 14 are rejected as being anticipated by US Patent Application Publication No. 2002/0151018 (Prouty). The examiner states that Prouty discloses 21- and 22-mer oligonucleotide primers fully complementary to SEQ ID NO: 3 and meets all of the structural requirements of the claims.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

Prouty discloses two sequences that are complementary to various regions of SEQ ID NO: 3. One of Prouty's sequences, called a common antisense oligonucleotide (page 5, col. 1, line 14-16) is structurally similar to Applicants' antisense SEQ ID NO: 11 and should hybridize to nucleotides 70 to 91 of SEQ ID NO: 3. Prouty's PCR primer sequence (page 5, col. 1, line 32) is complementary to nucleotides 242-262 of Applicants' SEQ ID NO: 3. Neither of these sequences was tested or reported by Applicants to inhibit expression of SEQ ID NO: 3.

Applicants' amended claims are now limited to compounds that bind SEQ ID NO: 3 between nucleobases 771 to 843 or 1011 to 5040 thereof, which sequences fall outside of the sequence of SEQ ID NO: 3 to which the Prouty's sequences can hybridize. In Table 1, Applicants demonstrate a selection of sequences that bind to the claimed regions of SEQ ID NO: 3 *to which Prouty's sequence cannot bind* and demonstrate inhibitory activity of 10% or above. Therefore, Prouty's two sequences cannot anticipate the presently claimed invention.

In view of these comments and the claim amendments noted above, this rejection may be properly withdrawn.

Rejections Under 35 USC §103(a)

Claims 1-2 and 4-15 are rejected under 35 USC §103(a) as being unpatentable over the following *combination of documents:*

(1) International Patent Publication No. WO 00/09754 (Stenn)

(2) Milner et al, **1997** *Nat. Biotech., 15*:537-541 (Milner)

(3) US Patent No. 5,801,154 ("Baracchini").

> The examiner states that one skilled in the art would have been motivated to modify the vector expressing an antisense oligo targeted to a nucleic acid encoding human stearoyl CoA desaturase, as taught by Stenn, about 8-50 nb as taught by Baracchini, modify the antisense compositions, and formulate them into compositions as taught by Baracchini. Further since methods of screening for antisense to a known gene was routine as taught by Milner, the person of skill would have been expected to find antisense that inhibits express of the desired enzymes because its sequence was known.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

A. Stenn's primer does not refer to antisense sequences, nor antisense sequences to human stearoyl CoA desaturase, nor specifically antisense sequences to the claimed target region of the enzyme.

Stenn does not specifically disclose or suggest an antisense oligonucleotide targeted to nucleobases 771-843 or 1011 to 5040 of a nucleic acid encoding human stearoyl CoA desaturase SEQ ID NO: 3. As discussed above, Stenn refers to a primer sequence that, when compared with Applicants' target SEQ ID NO: 3, happens to have a structure that should hybridize specifically to nucleobases 860-882 of SEQ ID NO: 3. Stenn provides no suggestion that its primer sequence is an antisense sequence, or that such a sequence would effect the enzymatic activity of the desaturase enzyme. Stenn suggests nothing about any other sequences that would hybridize to any other portion or region of SEQ ID NO: 3. Thus, Stenn teaches nothing about the subject matter of Applicants' amended claims.

B. The two secondary references teach nothing about human stearoyl CoA desaturase and are generic teachings referring to antisense technology.

The remaining two cited secondary documents teach nothing regarding human stearoyl CoA desaturase or antisense sequences capable of inhibiting that enzyme's activity, nor antisense sequences targeted to a specific region of SEQ ID NO: 3. Baracchini refers to antisense compounds that modulute another *completely unrelated protein* to human stearoyl CoA desaturase, namely multidrug resistance-associated protein (MRP). Milner is a review article that refers simply to assays for selecting antisense reagents in general. Milner does not suggest any antisense sequence to human stearoyl CoA desaturase, nor any antisense sequence to a particular region of that enzymes, much less the antisense sequence and target region of Applicants' claimed invention.

The secondary references do not even mention the protein human stearoyl CoA desaturase. They do not teach or suggest anything about the protein human stearoyl CoA desaturase. These references do not teach or suggest any antisense sequences to human stearoyl CoA desaturase or to any portion of human stearoyl CoA desaturase. Without any disclosure of human stearoyl CoA desaturase, neither Milner nor Baracchini can provide any suggestion that permits one to identify or suggest any specific human stearoyl CoA desaturase sequences as target sequences for binding by an antisense sequence, as required by claim 1. Neither Milner nor Baracchini teaches or suggests a utility for antisense compounds that bind human stearoyl CoA desaturase. These secondary references are discussed merely for their essentially duplicate, generic teachings related to antisense compounds.

C. The combination of documents does not make out a prima facie case of obviousness.

Applicants respectfully submit that an obviousness rejection based on a combination of documents

that disclose:

(1) a primer sequence that happens to structurally hybridize to nucleobases 860-882 of SEQ ID NO: 3; and

(2) documents cited merely to disclose generic antisense teachings or to disclose antisense sequences to unrelated proteins (i.e., Milner and Baracchini)

does ***not*** make a *prima facie* case of obviousness with regard to the pending amended claims.

Taking each reference as a whole, this combination does not provide any *suggestion* of the specific inhibitory antisense sequences of claim 1. Nothing in this combination even suggests that it would be "obvious to try" to make antisense compounds to target other regions of human stearoyl CoA desaturase, simply because others have made antisense compounds to other ***non-related*** proteins. The US patent law has long held that the "obvious to try" standard is not the appropriate standard for a determination of patentability.

In fact, Stenn does not refer to antisense technology at all, and thus does not assist in making a suggestion to try to make antisense sequences to SEQ ID NO: 3.[1] The only motivation to perform such a combination of components is derived from Applicants' disclosure. The mere fact that the prior art may be modified in the manner suggested by the examiner does not make the modification obvious, unless the prior art *suggested* the desirability of the modification. As discussed above,

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1 *In re Oetiker*, 977 F2d 1443, 24 USPQ 2d 1443, 1446 (Fed. Cir. 1992) "There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge cannot come from the applicant's invention itself."

the prior art references in combination and taken as a whole do not suggest the claimed invention.

Applicants' amended claims are not claiming "how to make" generic antisense compounds. Applicants' claims are directed to novel antisense compounds that are neither taught nor suggested by these references in combination. Nor does such a combination provide any prediction of success with respect to antisense sequences to human stearoyl CoA desaturase as the target. See, e.g., SEQ ID NOS: 21, 34-36, 38, 40 and 41, which display no inhibitory activity in Table 1. Thus, the cited references, taken together as a whole, do not make obvious the presently claimed invention.

It is only Applicants who have shown antisense sequences that hybridize with sequences within certain regions of human stearoyl CoA desaturase and display inhibitory activity of at least 10% in a suitable assay.

In view of the above amendments and these remarks, Applicants' respectfully request that the examiner withdraw the outstanding rejections and permit the above pending claims to pass to issue in due course.

The Director is hereby authorized to charge any additional fees required with the filing of this paper or credit any overpayment in any fees to our deposit account number 08-3040.

Respectfully submitted,

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